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Review

Nutrition, dietary habits, and weight management to prevent and treat patients with peripheral artery disease

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Peripheral artery disease (PAD) affects 3%-10% of the Western population and if remains untreated can have devastating consequences to patients and their families. This review article analyzes how healthy dietary habits can decrease PAD rates when applied in the general population. The aim is to focus on dietary, nutritional and weight management interventions in patients with established PAD. Most adults with PAD are overweight or obese, while three out of four patients are characterized by deficiencies in vitamins and minerals. Weight loss interventions when needed and specialized dietary plans should be routinely recommended in patients with PAD. Appropriate nutritional support is of paramount importance in patients with advanced stages of PAD (critical limb ischemia).

Keywords

Peripheral artery disease; critical limb ischemia; nutrition; diets; weight loss; prevention; treatment

1. Introduction

Peripheral artery disease (PAD) is defined as partial or complete stenosis of $\geq$ 1 peripheral arteries (Criqui and Aboyans, 2015). PAD prevalence ranges between 3%-10%, but it can be as high as 15%-20% among elderly (Nosova et al., 2015). More than 65% of adults with PAD are overweight or obese, while 78% are characterized by deficiencies in vitamins and minerals (Thomas et al., 2019). Both suboptimal nutritional status and high fat mass have been associated with worsening of the ambulatory status and vascular health in patients with PAD and claudication (Gardner et al., 2011). Nutritional advice and weight management are of paramount significance in PAD management (Hirsch et al., 2001). Primary prevention with emphasis on healthy nutritional habits may be advantageous in terms of decreasing rates of PAD, whereas a secondary prevention approach can be useful in slowing PAD progression and improving claudication symptoms (Unkart et al., 2019).

Pre-existence of coronary or cerebrovascular atherosclerosis, hypertension, diabetes mellitus, smoking, population minorities and advancing age, are all associated with PAD (Fowkes et al., 2013; Joosten et al., 2012; Selvin and Erlinger, 2004). PAD ranges from asymptomatic to symptomatic, while among multiple classifications, the Rutherford classification is the most commonly used to categorize PAD patients according to their symptoms. Asymptomatic PAD is defined as Rutherford Stage 0, while patients presenting with mild or moderate claudication, or walking-induced leg muscle pain relieved by rest, are classified as Stages 1 and 2, respectively. In later stages of PAD, patients exhibit foot pain at rest (Stage 4), and/or ulcers and gangrene (Stages 5 and 6) (Anderson et al., 2013; Hossain et al., 2019; Kullo and Rooke, 2016).

American Heart Association (AHA) recommends ankle brachial index as the initial diagnostic test for PAD (Alahdab et al., 2015). The Edinburg Artery Study showed that only 15% of patients with ankle brachial index ≤ 0.90 -which is diagnostic for the disease- experience intermittent claudication, whereas almost 35% reported no symptoms (Campia et al., 2019). Farah et al. showed that the walking capacity of 133 patients with PAD fluctuated accordingly to their comorbidities, with diabetes and coronary artery disease being independent predictors of their ambulatory status (Farah et al., 2013). Untreated or inadequately treated PAD may lead to critical limb ischemia (CLI) or even amputation (Leng et al., 1994). CLI is characterized by chronic ($\geq$ 2 weeks) ischemic rest pain, non-healing wound/ulcers, or gangrene in one or both legs, attributable to proven arterial occlusive disease (Kokkinidis et al., 2020c). A small percentage of patients with PAD, will develop finally CLI and will have much higher risk for amputation and mortality compared to claudicants. It is striking that the one-year risk of limb loss is 30% and the five-year all-cause mortality is 50% in patients with CLI (Kokkinidis and Armstrong, 2020; Kokkinidis et al., 2020b; Norgren et al., 2007). Coronary artery disease and PAD share a common pathogenesis and risk factors for development (e.g., smoking, dyslipidemia, hypertension, and diabetes mellitus) (Bhatt et al., 2006). Plaque rupture or erosion can provoke superimposed atherothrombosis and subsequent vessel occlusion, leading to cardiovascular (CV) events, including myocardial infarction (MI), stroke, limb ischemia, and CV death (Bauersachs and Zannad, 2018). Thus, prognosis can be improved through secondary prevention measures, with lifestyle changes, medicinal control of modifiable CV risk factors, and the prevention of blood clot formation with antithrombotic therapies (Cortés-Beringola et al., 2017). The purpose of this review is to present the current evidence regarding the association between healthy nutrition, weight management and specific targeted nutritional habits with PAD risk, progression, and outcomes.

2. Role of nutrition and dietary habits in prevention of peripheral artery disease and other atherosclerotic cardiovascular diseases

Atherosclerosis is characterized by chronic systematic low-grade vascular inflammation (Hansson and Hermansson, 2011). Accumulation of lipids and inflammatory cytokines damage the vascular endothelium, provoking the atherosclerotic plaque formation (Insull, 2009). Metabolic disorders and unfavorable lipid profiles have been found to promote atherogenesis by increasing oxidized low-density lipoprotein (oxLDL) (Badimon et al., 2009). Although emphasis is given mainly on reducing LDL-cholesterol (LDL-C)-by the restriction of saturated fat, trans-fat and cholesterol- there are also other beneficial dietary complements that could slow down the atherosclerosis progress (Torres et al., 2015). A recent study tried to demonstrate the main determinants of diet quality showing that being male, having low income, living with other people, physical inactivity, and current smoking were generally the main factors associated with a diet low in fruits, vegetables, legumes, wholegrains as well as nuts and seeds (Maugeri et al., 2020). The Global Burden of Disease (GBD) Study analyzed the relationship between single dietary risk factors and cardiovascular diseases (CVDs) (Meier et al., 2019). According to the GBD more than 9.1 million deaths from CVDs worldwide are attributable to dietary risks (Global Burden of Disease Cancer et al., 2019). Therefore, optimized dietary patterns might assist to overcome the burden of CVDs. In terms of food and nutrient groups, five risk factors had an attributable fraction greater than 10% of the total diet-related CVD burden: diet low in whole grains (20.4%), diet low in nuts and seeds (16.2%), diet low in fruits (12.5%), diet high in sodium (12.0%), and diet low in seafood omega-3 PUFA (10.8%) (Meier et al., 2019).

The dietary intake of polyunsaturated fatty acids (PUFA) is vital, as they cannot be synthesized *in vivo*. The main sources of PUFA are fatty fish (herring/mackerel and salmon/whitefish/char), flax seeds and nuts -omega-3- as well as vegetable oils (safflower oil, peanut butter, avocado oil etc.) and animal fat -omega-6- (Wall et al., 2010). Omega-3 PUFAs regulate blood pressure and the thrombosis response. They are involved in inhibiting eicosanoids production and result to blunted arterial wall inflammatory response (Wall et al., 2010). The American Heart Association (AHA) recommends a weekly intake of $\geq$ 200 mg omega-3 (2 portions/week of fatty fish or oral omega-3 supplements) (Rimm et al., 2018). Controversy exists in the literature regarding the role of n-6 fatty acids in CVD prevention. A diet containing an excess of 10% n-6 fatty acids has been evoked to induce adverse effects against CVD, mostly due to their proinflammatory and oxidation effects (Patterson et al., 2012). It is suggested that dietary n-6 fatty acids may increase oxidation susceptibility of LDL-C and VLDL-C (Hammad et al., 2016; Russo, 2009). High intake of n-6 PUFA might also be associated with increased vasospasm, vasoconstriction, and blood viscosity (Hammad et al., 2016). However, not all omega-6 PUFA have negative effect in the progression of the disease, and AHA recommends lower consumption of anti-atherogenic omega-6 PUFA, such as dihomo-γ-linolenic acid (DGLA), which can be metabolized to prostaglandin E1 (Das, 2008). Butyrate is a short-chain fatty acid which is produced by the fermentation of fibers from the gut microbiota in intestine. Studies on mice fed with 1% butyrate showed that it can reduce the pro-inflammatory cytokines (IL-1β, IL-6, and TNF) and nitric oxide production in small and stable atherosclerotic lesions (Aguilar et al., 2014; Menzel et al., 2004).

Plant-based diets have been associated with potential benefits in cardiovascular health. Phytosterols, steroids of similar structure with cholesterol, are associated with lower plasma LDL-C levels, achieved via altering the expression of ABCA1 (upregulation) (Andersson et al., 2004; Katan et al., 2003). A consumption of 2 g/daily of phytosterols and flavanols is recommended (Sabeva et al., 2011). Fruits and vegetables are the main sources of flavanols, with catechin (present in green tea and cocoa) being the main representative of the cluster (Falcone Ferreyra et al., 2012). They can reduce the production of pro-inflammatory cytokines and chemokines by the vascular endothelial cells. Similarly, hydrogen sulphide (H_2S), a derivative of allicin -a secondary garlic metabolite-, can reduce the leukocytes adherence in the arterial wall and the formation of foam cells (Yamakuchi et al., 2008).

Recent large cohort studies support that Mediterranean Diet is effective both in primary and secondary prevention of cardiovascular events (Martínez-González et al., 2015; Ruiz-Canela and Martínez-González, 2014). This is probably achieved via oxida-

tive stress reduction. Numerous polyphenol compounds in olive oil exert anti-inflammatory effects, including oleuropein, tyrosol, and hydroxytyrosol (Martinez-Gonzalez et al., 2018; Massaro et al., 2010). The EUROLIVE study revealed that the consumption of virgin olive oil can reduce oxidative stress and triacylglycerols levels while increasing the levels of high-density lipoprotein (HDL)-cholesterol in serum plasma (Covas et al., 2006).

Among vitamins, vitamin E and C as well as supplementation with potassium, zinc and magnesium have been shown to have a cardioprotective role. The underlying protective mechanism is based on oxidative stress reduction, stabilizing in this way the atherosclerotic plaque and regulating the fluctuation of blood pressure (Ashor et al., 2014; Honarbakhsh and Schachter, 2009; Villacorta et al., 2003). Folate and vitamin B (B2, B6, B12) can decrease homocysteine levels which has been linked to increased proliferation of vascular smooth muscle cells and collagen synthesis (Hustad et al., 2000). Homocysteine is additionally interfering with the vascular integrity via induction of endothelial dysfunction and reduction of arterial wall elasticity (Hustad et al., 2000; Lin et al., 2012).

PAD prevalence was higher in patients who consumed greater amounts of saturated fats, meat, and animal products. On the contrary, foods rich in fiber, such as cereal fiber, as well as antioxidants (vitamins A, C, E) and polyunsaturated fats have a protective role in PAD (Fontana, 2018; Nosova et al., 2015). Down-regulation of vitamin B6, B12 and folic acid levels - all of each involved in homeostasis of homocysteine - could increase PAD risk (Fenton et al., 2016). More specifically, the conversion of homocysteine to cystathionine -derivative of homocysteine- is vitamin B6-dependent, whereas re-methylation requires the co-factors folate and vitamin B12 (Blom and Smulders, 2011). Folate deficiency might contribute to a decreased ability to maintain homocysteine homeostasis and potentially lead to a toxic accumulation of unmetabolized homocysteine in the serum (Booth et al., 2004). This deficiency is associated with endothelial dysfunction, vasoconstriction, and endovascular inflammation (Dionisio et al., 2010).

3. Diets

3.1 Mediterranean diet

Mediterranean Diet has been associated with lower rates of PAD and improvement of claudication symptoms (Ruiz-Canela and Martínez-González, 2014). Mediterranean diet is characterized by generous amounts of olive oil as the main culinary fat and is characterized by high consumption of plant-derived foods (fruit, vegetables, legumes, nuts and seeds, and whole grain cereals); frequent, but moderate intake of - mainly red - wine with meals; moderate consumption of seafood and dairy products (especially yogurt and cheese, but not whole milk, butter or cream), poultry and eggs; and low consumption of sweet desserts, red and processed meats (Ruiz-Canela and Martínez-González, 2014). The PREDIMED study showed a significant relative risk reduction in type 2 diabetes mellitus (40%), PAD (64%) incidence and other cardiovascular complications (30%) in patients following a Mediterranean diet. Olive oil consumption seems to be superior to nuts oil in terms of cardiovascular outcomes (Martínez-González et al., 2015; Ruiz-Canela and Martínez-González, 2014). Dietary advice can be helpful for the prevention of PAD in diabetics, even in populations traditionally accustomed to Mediterranean dietary habits (Ciccarone et al., 2003). High adherence to this dietary pattern was not only associated with low prevalence of obesity and hypertension, but also decreased the odds of concentric left ventricle hypertrophy. Mediterranean diet was proved to increase ventricular filling, which in turn increased end-diastolic filling, left ventricular volumes, stroke volume, and ejection fraction (Maugeri et al., 2019). Data from the Kardiovize Brno cohort showed that high adherence to the prudent dietary pattern was associated with lower odds of abdominal obesity, abnormal glucose concentration, and metabolic syndrome. This finding is of clinical impact in primary prevention for cardiovascular events (Levitan et al., 2016).

3.2 Plant based-vegetarian-vegan diets

Vegetarian diets are followed by more than 5% of the population and have been recognized as potentially cardio-protective (Delaney et al., 2019). Vegetarian diets emphasize the consumption of fruits, vegetables, nuts and grains with limitation of dairy or meat products (Delaney et al., 2019). Vegeterians are less prone to diabetes mellitus, hypertension, hypercholesterolemia and mortality from ischemic heart disease and stroke (Delaney et al., 2019). Given the low content of fat, cholesterol, salt and red meet, vegetarian diet may decrease vascular endothelial cell injury (Rathod et al., 2016). Polyphenols may decrease oxidation of LDL and prevent oxidized LDL (OxLDL)-induced monocyte adhesion to vascular endothelial, monocyte transformation into macrophages, and foam cell formation. Reducing red meat intake may decrease trimethylamine-N-oxide (TMAO) formation (Salomon du Mont et al., 2017). Decreasing TMAO formation inhibits atherogenesis by down-regulating macrophage uptake of OxLDL (Tuso et al., 2015). The Vegan diet has become more popular recently but its benefit on cardiovascular outcomes is still debated, given the negative effect on the vascular epithelium (Ruiz-Canela and Martínez-González, 2014; Wischmeyer et al., 2018).

3.3 Ketogenic diet

Ketogenic diet is based on a reduction in carbohydrates (usually less than 50 g/day) and a relative increase in the proportions of proteins and fats (Ciccarone et al., 2003). A stricter version is the very-low-carbohydrate ketogenic diet, where carbohydrates are limited to less than 30 g/day (Ciccarone et al., 2003). The inadequate glucose storage leads to ketone bodies production to cover the energy needs of central nervous system (Veech, 2004). A recent meta-analysis showed that ketogenic diet is associated with reduction of body mass index (BMI), abdominal circumference, both systolic and diastolic blood pressure, triglycerides levels, fasting plasma glucose and HbA1c, and increase in HDL- cholesterol levels (Rathod et al., 2016). Nonetheless, no significant benefit was reported on the prevention of cardiovascular events in the follow-up (Naude et al., 2014). Adverse events of ketogenic diet include but are not limited to kidney stones, osteoporosis, and impaired growth (Bueno et al., 2013).

3.4 Intermittent fasting diet

In a recent statement AHA analyzed the intermittent fasting program benefits in cardiovascular health (Tinsley and Horne, 2018). Intermittent fasting program is based on alternate-day (ADF) or periodic fasting (PF) for weight loss. Benefits include reductions in total cholesterol (-6 to 21%), LDL cholesterol (-7

to 32%) and triglycerides (-16 to 42%) as well as systolic blood pressure (3 to 8%) and diastolic blood pressure (6 to 10%) (Tinsley and Horne, 2018). Furthermore, a weight reduction of 3-8% over a course of 3-24 weeks has been reported to decrease the risk of type 2 diabetes and the production of atherosclerotic inflammatory cytokines (Tinsley and Horne, 2018). The potential mechanisms associated with these beneficial effects include improved insulin sensitivity, increased levels of fibroblast growth factor 21, reduced inflammation and oxidative stress, and enhanced cellular and molecular adaptive stress responses. However, it is difficult to understand whether fasting directly affects cardiovascular markers or its benefits depend on weight loss (Mattson et al., 2014; Planavila et al., 2013). On the other hand, it can be associated with frequent fractures due to osteoporosis in elderly patients (Dardano et al., 2014). The caloric restriction often leads to reactive hypoglycemia which is detrimental for patients using diabetic medications. A study in 2018, analyzed the way that frequency and timing of meals may affect cardiovascular health outcomes (Agodi et al., 2018). It is suggested that skipping breakfast or the afternoon snack may adversely affect the circadian clock and correlates with increased postprandial glycemic response, triglycerides level and total cholesterol/HDL-C ratio. These are risk factors for poor cardiovascular health, while higher eating time interval and frequency may promote a more ideal cardiovascular profile (Agodi et al., 2018). More data are needed in terms of overall safety and cardiovascular risk reduction of patients who follow an intermittent fasting program (Malinowski et al., 2019) (Table S1).

4. Importance of dietary habits and nutrition in patients with established peripheral artery disease

Dietary habits are a cornerstone in the development and progression of PAD (Hirsch et al., 2001). Combined nutrition and exercise interventions reduce walking impairment compared to patients practicing exercise alone (Fahrleitner et al., 2002; Wang et al., 2008). During the last decade, multiple interactions between medications used for medical management of PAD and dietary constituents have been reported. Deficiencies such as Q10 Coenzyme- which supplementation can be cardioprotective-, zinc, and vitamin B12 interact with lipid lowering medications, antihypertensive drugs and oral hypoglycemic agents, respectively (Booth et al., 2004; Fenton et al., 2016). Similarly, increased levels of vitamins K and E, with parallel administration of warfarin as anticoagulation therapy for PAD's comorbidities, have been associated with vascular calcification. Thus, patients on coumadin should be routinely monitored for these nutrient deficiencies and at the same time evaluated for candidacy for newer oral anticoagulants (Foley et al., 2017; Kokkinidis et al., 2020a; Siasos et al., 2020). Novel oral anticoagulants in combination with aspirin may provide an alternative treatment in PAD, however, it is deemed necessary to identify patient subgroups who will benefit the most (Koutsoumpelis et al., 2018). Hypovitaminosis D has been associated with higher prevalence and severity of PAD disease. The potential mechanism is explained by the fact that hyperparathyroidism increases the risk of osteomalacia and arterial calcification (Krishna, 2019). Folate and vitamin D deficiencies have been linked to an increased risk of PAD and worsening ambulatory status (Kokkinidis et al., 2020a). The Institute of Medicine's Food and Nutrition Board recommends consumption of 700 IU/day of vitamin D, 400 μg/day folate, 1.7 mg/day vitamin B6, 2.4 μg/day vitamin B12 and a daily maximum of 1250 mg sodium in patients with PAD (Nosova et al., 2015) (Table 1).

CLI is characterized by significantly increased levels of atherosclerotic inflammatory cytokines when compared to intermitted claudication (Jalkanen et al., 2016). CLI has a 25% risk of mortality and 30% of major limb amputation within 12 months from its diagnosis (Kokkinidis and Armstrong, 2017; Norgren et al., 2007). Patients with CLI often present with ulcers and muscle atrophy (Kinlay, 2016). Ischemic ulceration exacerbates protein loss which is estimated to be as high as 100 g per day (Russell, 2001). Thus a correction of 10% is recommended to the estimated energy requirements in patients with CLI (Harris-Benedict equation) (Cereda et al., 2011). Deficiencies of vitamin A, vitamin C, vitamin D and E as well as zinc and selenium have been all found to have negative effects on wound healing, given that when present, they all augment the healing process (Chua et al., 2011; Mirastschijski et al., 2013). Patients with malnutrition and CLI have the highest mortality risk in the first 30 days post amputation (Delaney et al., 2019). Patients with ischemic ulceration or rest pain often undergo revascularization to avoid amputation (Salomon du Mont et al., 2017). Due to the catabolic state occurring after limb loss, post-amputation patients have an even higher increase in the energy levels requirements. Appropriate supplementation of energy, protein and micronutrients is essential (Wischmeyer et al., 2018). The systemic nature of the disease is prevalent and its manifestations seem to vary. The incidence of renal artery stenosis is increased in patients with PAD. This diagnosis must therefore be kept in mind when hypertension resistant to medical therapy is encountered in these patients. The optimal blood pressure for patients with PAD without diabetes mellitus is 140/90 and 130/80 for patients with diabetes or chronic kidney disease (Singer and Kite, 2008). Upper extremity artery disease due to atherosclerosis is mostly situated at the level of the brachiocephalic trunk and the subclavian and axillary arteries (Aboyans et al., 2007). While the vast majority of strokes presented secondary to carotid and vertebral artery disease than cardioembolism (Donnan et al., 1998).

5. Weight changes and atherosclerotic cardiovascular disease

The AHA recently established the concept of the AHA Life's Simple 7 (LS7) metrics based on four healthy behaviors (non-smoking, normal weight, moderate physical activity, and a healthy diet) and three health factors (normal cholesterol, blood pressure, and fasting blood glucose) (Ogunmoroti et al., 2018). Weight status constitutes a significant role in the progression of atherosclerotic disease (Neeland et al., 2019). Overweight status and obesity are characterised by excessive expansion of white adipose tissue (WAT) mass (Lempesis et al., 2020). The pathophysiology of obesity and its complications, however, is not only driven by the increase in WAT mass, but mainly by the dysfunctional status of the organ, also known as adiposopathy (Blüher, 2013; Goossens, 2008, 2017; Goossens and Blaak, 2015; Lempesis et al., 2020). Adiposopathy is comprised by adipocyte hypertrophy, decreased adipose tissue blood flow, altered oxygen levels within the tis-

Table 1. Diet and lifestyle recommendations for Peripheral Artery Disease prevention.

Diet				Lifestyle
Fats	**Proteins**	**Trace & Elements**	**Fruits, Vegetables & Anti-Oxidants**	
• Saturated fats to < 7% of daily caloric intake. • Increase the consumption of omega-3 fatty acids. • At least two fish meals per week. • Olive oil for cooking. • High unsaturated fat content and the anti-oxidant hydroxytyrosol. • Consume low-fat dairy products. • Limit red meat to one meal per week. • Replace with beans or legumes.	• Adjust requirement if hypermetabolic state. • Variable adjustment depending on presence/size of ulceration/ peri-operative state (magnitude of surgery performed)/ active infection.	• Vitamin D = 700 IU/day • Folate acid = 400 μr/day • Vitamin B6 = 1.7 mg/day • Vitamin B12 = 2.4 μg/day • Daily maximum of 1250 mg sodium • Higher intake of Vitamins A, C, E and Zinc	• Five serves of vegetables, two serves of fruit, four serves of wholegrain per day. • Consume wholegrain in preference to white or refined grain products. • 1–2 cups of green tea daily.	• Avoid tobacco use. • Regular physical activity. • Minimum of 30 min moderate intensity physical activity at least 5 days/week.

sue, a state of chronic low-grade inflammation and blunted lipid metabolism (Frayn and Karpe, 2014; Goossens and Blaak, 2015; Shulman, 2014). The later includes impaired capacity to store the surplus of dietary lipids, resulting to deposition of ectopic fat - fat accumulating in body locations where it is not physiologically stored, like liver and muscle-, and a shift to visceral adipose tissue (fat storage in the intraperitoneal and retroperitoneal spaces), contributing to increased circulating free fatty acids, oxidative stress, systematic inflammation, adipokine dysregulation and insulin resistance (Bays, 2012; Frayn and Karpe, 2014; Goossens and Blaak, 2015; Lempesis et al., 2020; Shulman, 2014). Thus, presence or absence of adiposopathy can partially explain the heterogeneity of obesity and its manifestations, through modulation of risk factors such as diabetes mellitus, hypertension and dyslipidemia (Bays et al., 2008).

Weight loss should be recommended for all obese and overweight patients. The initial goal is 5% to 10% weight reduction in the first 6 months (Jensen et al., 2014). The Diabetes Prevention Program study randomized 3,234 patients in three clusters: 1) Intensive lifestyle intervention (ILI) group, 2) metformin group and 3) placebo group. The mean weight loss after a 2,8 years' follow-up was 5.6, 2.1 and 0.1, respectively. The first and the second group had a reduction of the incidence of diabetes by 58% and 18%, compared to placebo (Diabetes Prevention Program Research Group , 2009; Knowler et al., 2002). Similarly, the Look AHEAD trial presented that ILI patients had a greater reduction in glycosylated hemoglobin (HgA_{1c}) and a more favorable blood pressure and lipid profile (Gadde et al., 2018). Weight loss achieved with diet and exercise improves cardiometabolic risk factors, reduces the incidence of diabetes, dyslipidemia, and achieves glycemic and blood pressure control (Look AHEAD Research Group et al., 2013). In conclusion, weight management effectively reduces the atherosclerosis progression via downregulating risk factors such as diabetes mellitus, hyperlipidemia, hypertension and adiposopathy (Gadde et al., 2018).

6. Weight changes and peripheral artery disease

The current gold-standard intervention to improve walking performance in patients with intermittent claudication is supervised exercise, followed by active monitoring of nutrition status (Kokkinidis et al., 2019). Targeting weight loss has been associated with less decline in 6-minutes-walk test (Tinsley and Horne, 2018). Polonsky et al. showed that compared to patients with weight gain, patients with intentional weight loss $>$ 5 pounds had less annual decline in 6-minutes-walk distance, despite losing greater muscle calf area (Polonsky et al., 2019). A meta-analysis of 3 weight-loss trials based on calorie restriction with physical activity showed that every 1-kg loss of fat mass predicted a 0.01-m/s increase in walking speed, independently of losing lean mass (Beavers et al., 2013). The potential mechanism is the exacerbation of a low grade inflammatory response triggered by the increased visceral fat around skeletal muscles and the genetic downregulation of mitochondrial gene leading to dysfunction (Sparks et al., 2005; Tzoulaki et al., 2005). Thus, emphasizing weight reduction in early stages of the disease decreases mortality rates and improves the quality of life, avoiding the detrimental effects of sarcopenia in later stages (Kokkinidis et al., 2019).

The obesity paradox is based on observations of overweight and obese patients with established PAD, who had better prognosis compared to their non-overweight/non-obese peers (Miller et al., 2012; Palaiodimos et al., 2020). This may be explained by the fact that a significant percentage of the underweight elderly patients, suffered from frailty and sarcopenia. Sarcopenia is defined as an unintentional loss of lean muscle mass, frequently associated with aging. Sarcopenic-lean and sarcopenic-obese patients are two

distinct sarcopenia groups. Preservation of muscle mass in collaboration with myokines and circulating hormones influence the progression of PAD (Addison et al., 2018). Almost 25% of patients with intermittent claudication have sarcopenia and those patients tend to have a worse walking performance compared to their non-sarcopenic peers (Kokkinidis et al., 2019). The obesity paradox has potential implications on CLI as well. Higher BMI is associated with lower rates of mortality in patients with lower extremities ulcers (Kinlay, 2016). On the other hand, obese patients with CLI often belong to the subtype of sarcopenic-obesity, suffering from both muscle atrophy and obesity related complications (Tzoulaki et al., 2005). Sarcopenia increases platelet dysfunction, promoting hypercoagulable states and impairs wound healing by the expression of atherosclerotic cytokines (Hicks et al., 2018; Sugai et al., 2018). Sarcopenia has been associated with higher rates of incomplete wound healing, amputation, major adverse cardiovascular events, major adverse limb events and mortality (Kokkinidis et al., 2020d; Miller et al., 2012). Timely wound healing is of utmost importance as far the outcome of the procedure is concerned (Chi et al., 2019; Wischmeyer et al., 2018).

7. Conclusion and future perspectives

Patients with PAD and CLI are nutritionally vulnerable groups and subsequently, nutritional support, emphasis on proper diet and close monitoring of weight are prerequisites for optimal outcomes. Population level interventions can decrease the prevalence of PAD, while at the same time, early aggressive medical management with emphasis on the aforementioned in patients with PAD, can likely improve the pain free walking distance, quality of life, survival, while decreasing functional decline, amputation and overall mortality rates in these individuals. FOURIER trial showed that low-dose antithrombotic therapy with aspirin and lipid lowering -with a PCSK9 inhibitor- are associated with reduction of both cardiovascular and limb adverse events (Bonaca et al., 2018). Furthermore, analyses of HOPE trial have demonstrated that using statins and ACE-Is reduce cardiovascular risk in patients with PAD, with less clear effects with antiplatelet therapies. Implementation of these therapies remains challenging because of the cost and the burden of polypharmacy. Further studies are necessary to identify the patients with PAD who will benefit the most from these advances (Heart Outcomes Prevention Evaluation Study Investigators et al., 2000). While further research attempts are anticipated, emphasis on proper nutrition, dietary interventions and weight management should be part of the PAD multidisciplinary team (primary care physicians, cardiologists, endocrinologists, nutritionists and dieticians, podiatrists and vascular interventionalists) that participates in the care of those patients.

Authors' Contributions

All authors contributed to conception, design, and writing of the manuscript.

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Conflict of Interest

Carlos Mena: Consultant for Abbott, Boston Sci, COOK, Medtronic, Cardinal Health and Optum Labs.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm.2020.04.202.

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